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(54) Title: SOLUBILIZED PHARMACEUTICAL COMPOSITION FOR PARENTERAL ADMINISTRATION

(57) Abstract

The invention refers to an aqueous pharmaceutical composition for parenteral use, said composition comprising i) as active substance a vitamin D or a vitamin D analogue having a solubility in water of ≤0.1 % w/v at room temperature, and which is susceptible to gradation in an aqueous acidic environment, ii) a non–ionic solubilizer capable of solubilizing said active substance, the solubilizer being a low histamine–releaser and containing a fatty acid ester of polyethylene glycol optionally in admixture with a polyethylene glycol and having no negative effect on the stability of the active substance in the final composition determined as described herein, and iii) an aqueous vehicle. Moreover, this invention refers to the use of a polyethylene glycol ester as a non–ionic solubilizer.

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SOLUBILIZED PHARMACEUTICAL COMPOSITION FOR PARENTERAL ADMINISTRATION

Field of the invention

The present invention concerns aqueous pharmaceutical compositions for parenteral use which contain a therapeutically and/or prophylactically active substance which has a low aqueous solubility. Furthermore, the active substance is susceptible to degradation in an aqueous acidic environment.

Background of the invention

An important route for administration of many drug substances is the parenteral route. Firstly, many drug substances are not sufficiently absorbed through the gastrointestinal mucosa to give a sufficient systemic concentration to obtain the desired therapeutic and/or prophylactic effect. Secondly, a relatively fast onset of a therapeutic effect is required in many cases and then parenteral administration of the drug substance in question is first choice, especially intravenous administration.

Compositions for parenteral use may be presented in the form of aqueous or oily solutions, dispersions, emulsions, suspensions, etc. Especially when a composition is to be administered intravenously, it is preferred that the composition is in the form of a solution. However, a number of drug substances have a very low solubility in water, i.e. in order to obtain an aqueous composition which is in the form of a solution, it may be necessary to use a solvent mixture containing water and one or more organic solvents, such as a conventional co-solvent composition containing ethanol-propylene glycol.

Another possibility is to employ a solubilizer such as, e.g. Cremophor® EL. However, parenteral administration of compositions containing Cremophor® EL has previously been found to give rise to release of histamine (Lorenz, W. et al. in Agents and Actions, 1 982, **12 1/2**, 64-80 and Ennis, M. et al. in Agents and Actions, 1 985, 16 3/4, 265-268). The resulting anaphylactoid reactions in man following the administration of drug substances dissolved in Cremophor@ EL, pose a significant clinical problem. Eschalier, A. et al., Cancer Chemother Pharmacol 1988;21(3):246-50, have shown that Cremophor EL and Tween 80, which is another pharmaceutical excipient used as a solubilizer, induce non-specific histamine release. Therefore, attempts have been made to identify and/or develop solubilizers which have essentially no histamine

release effect. Solutol® HS 15 manufactured by BASF, Germany, has been suggested as a solubilizer which is non-toxic and essentially without the unwanted histamine release effect, i.e. it is regarded as a low-histamine releaser.

Prior art compositions containing Solutol® HS 15 have a relatively high content of Solutol® HS 15 and, furthermore, other auxiliary components are included in the composition (e.g. emulsifiers, organic solvents, chelating agents, etc.). However, when developing pharmaceutical compositions - especially when developing compositions for parenteral use - it is an aim only to use non-toxic auxiliary substances which have a required function and only in the lowest possible amount to fulfil the required function. Therefore, there is still a need for developing compositions for parenteral use essentially without undesired histamine releasing side-effect, and wherein the content of solubilizer and other auxiliary substances is very low. This need is especially desired when developing compositions containing compounds having a very low solubility in water such as vitamin D or vitamin D analogues.

The present inventors have found that a solubilized aqueous pharmaceutical composition containing vitamin D or a vitamin D analogue as the drug substance can be obtained by using a relatively small amount of solubilizer and, where required or optionally, comparatively small amounts of auxiliary substances. Furthermore, such compositions are stable with respect to the chemical stability of the drug substance.

Summary of the invention

Thus, the present invention provides an aqueous pharmaceutical composition for parenteral use, said composition comprising as active substance a vitamin D or a vitamin D analogue having a solubility in water of ≤ 0.1% w/v at room temperature, and which is susceptible to degradation in an aqueous acidic environment, a non-ionic solubilizer capable of solubilizing said active substance, the solubilizer being a low histamine-releaser and containing a fatty acid ester of polyethylene glycol optionally in admixture with a polyethylene glycol and having no negative effect on the stability of the active substance in the final composition determined as described herein, and an aqueous vehicle.

The invention also relates to a method for the treatment of neoplastic diseases comprising administering to a patient in need thereof a composition according to the invention. Said neoplastic disease is preferably a hepatoma, a cancer of the pancreas, mamma, colon or prostata, or a hematological neoplastic disorder. The invention also relates to the use of Solutol® HS 15 (ME/DZ - D205, October 1996 solutol.doc,

Technishes Merkblatt, Solutol HS15, Polyethylene-660-Hydroxystearat als nichtionogener lösungsvermittler für Injektionslösungen, MEF 151 d, Januar 1986, or as more recently described in Technical Information ME 151 e (977) July 1998 (MPM) from BASF Fine Chemicals) as a stabilizing agent as well as to a method for preparing a composition according to the invention.

Detailed description of the invention

In the present context, the term "susceptible to degradation in an aqueous acidic environment" means that the degradation rate of the active substance is at least 5 times greater at an acidic pH (e.g. pH 4) than at a neutral-weakly alkaline pH (e.g. pH 8) and at a temperature of about 25'C. Said degradation has been observed with drug substances such as vitamin D and vitamin D analogues showing a correlation between decreasing pH and increasing velocity constant of degradation.

Furthermore, the term "no negative effect on the stability" is intended to mean that the degradation of the active substance in a composition according to the invention is at the most of the same order of magnitude or less than the degradation of the same active substance in a conventional co-solvent composition containing the same amount of active substance and having the same pH as that of the composition according to the invention. A suitable co-solvent composition for use in testing any effect on the stability is the co-solvent composition described in Example 3 herein, i.e. a co-solvent composition containing ethanol-propylene glycol in a weight ratio of from about 1:5 to about 1:10.

In the present context the term "stability" is intended to mean that after 3 months storage at 40°C, a degradation of the active substance of at the most about 10% w/w such as at the most about 6% w/w or at the most about 3% w/w of the active substance is observed.

In the present context the term "active substance" is intended to mean any biologically or pharmacologically active substance or antigen-comprising material; the term includes drug substances which have a therapeutic and/or prophylactic effect and which have utility in the treatment or prevention of diseases or disorders affecting mammals, including animals or humans, or in the regulation of any animal or human physiological condition, and it also includes any biologically active substance which, when administered in an effective amount, has an effect on living cells or organisms. The term "active substance" furthermore includes vitamins, nutrients and other substances which have a physiological effect on mammals. The term also includes

transport forms of the active substances such as, e.g., prodrugs, physiologically or pharmaceutically acceptable salts of the active substances and complexes of the active substances.

As mentioned above, an active substance for use in compositions according to the invention has a very low solubility in water. An example of a such substance is vitamin D or a vitamin D analogue.

Vitamin D analogues which are especially suitable for use in compositions according to the present invention are Seocalcitol [1(S),3(R)-dihydroxy-20(R)-(5´-ethyl-5´-hydroxy-hepta-1´(E),3´(E)-diene-1´-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene]; α-calcidol [1(S),3(R)-dihydroxy-20(R)-(4-methyl-pentyl)-9,10-secopregna-5(Z),7(E),10(19)-triene]; 1(S),3(R)-dihydroxy-20(R)-(5-ethyl-5-hydroxy-hept-1(E)-ene-3-yn-1-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene; calcipotriol; calcitriol [1(S),3(R)-dihydroxy-20(R)-(4-hydroxy-4-methyl-pentyl)-9,10-secopregna-5(Z),7(E),10(19)-triene]; tacalcitol [1α,24R-dihydroxy-vitamin D_3], 22-oxacalcitriol; OCT; maxacalcitol; 1α-hydroxy-vitamin D_2; 1α-hydroxyergocalciferol; 1α,25-dihydroxy-19-nor-vitamin D_2; paricalcitol; (7E,22E)-19-nor-9,10-secoergosta-5,7,22-triene-1α,3β-25-triol; 26,27-hexafluoro-1α,25-dihydroxy-vitamin D_3; falecalcitriol; 1α,24S-dihydroxy-vitamin D_2; 24R-ethyl-1α-hydroxy-vitamin D_3; and 1α-hydroxy-vitamin D_5 , as well as mixtures thereof.

Vitamin D analogues and vitamin D substances described herein have a solubility in water of 0.1% at the most, and are very slightly soluble to practically insoluble in water as described in Ph.Eur. 1997 general notices p. 3 and USP23 General notices p.10.

Other relevant substances are:

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-1-heptyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20(R)-(6-hydroxy-6-methyl-1-heptyl)-9,10-secopregna-5(2),7(E)-10(19)-triene;
1(S),3(R)-Dihydroxy-20(R)-(6-hydroxy-6-methylhept-1(E)-ene-1-yl-9,10)-secopregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20(R)-(6-ethyl-6-hydroxy-1-octyl)-9,10)-secopregna-5(Z),7(E),10(19)-triene;
1(S),3(R)-Dihydroxy-20(R)-(7-hydroxy-7-methyl-1-octyl)-9,10)-secopregna-5(2),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(7-hydroxy-7-methyloct-1(E)-en-1-yl-9,10)-sacopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6'-methyl-1'-heptyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-(5'-hydroxy-5'-methyl-1'-hexyloxy)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4'-hydroxy-4'ethyl-1'-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6'-hydroxy-1'-hexyloxy-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(5'-hydroxy-5'-ethyl-1'-heptyloxy)-9,10-seco-pregna-5(Z),7(E),10,19-triene;

1(S),3(R)-Dihydroxy-20(R)-(5'-hydroxy-5'-methyl-1'-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(5'-methyl-1'-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19-triene;

1(S),3(R)-Dihydroxy-20(R)-(4'-hydroxy-4'-(1"-propyl)-1'-heptyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4'-hydroxy-4'-methyl-1'-pentyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3'-hydroxy-3'-methyl-1'-butyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-(4-hydroxy-4-methyl-1-pentyl)-9,10-secopregna-(5Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-hydroxy-1-hept-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-(5-ethyl-5-hydroxy-hept-1(E)-en-1-yl),9,10-secopregna-5(2),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-(5'-hydroxy-5'-methyl-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(2),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-(5'-ethyl-5'hydroxy-hepta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-(6'-hydroxy-hexa-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene

1(S),3(R)-Dihydroxy-20-(5'-cyclopropyl-5'-hydroxy-penta-1'(E),3'(E)-dien-1'-yl)-9,10-secopregna-5(Z)-7(E),10,19-triene (5'(R) and 5'(S) isomers);

1(S),3(R)-Dihydroxy-20-(6'-hydroxy-6'-methyl-hepta-1'(E),3"(E)-dien-1'-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-(2-hydroxy-2-pentyl)-phenylmethoxy)-9,10-seco-progna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-(3-hydroxy-3-propyl)-phenylmethoxy)-9,10-seco-progna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-methyl-1-pentyloxymethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-methyl-1-pent-2-ynyloxymethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-hydroxy-4-trifluoromethyl-5,5,5-trifluoro-1-pent-2-ynyloxymethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-[3-(2-hydroxy-2-propyl)-phenoxymethyl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-hydroxy-3-ethyl-1-pentylthiomethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-hydroxy-3-ethyl-1-pentylsulphonylmethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-((1-hydroxy-1-methyl)ethyl)phenylthiomethyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3,3-difluoro-4-hydroxy-4-methyl-1-pentyloxymethol)-9,10-seco-pregna-5(Z)-7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(6'-ethyl-6'-hydroxy-oct-1'-yn-1'-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(7'-ethyl-7'-hydroxy-non-1'-yn-1'-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(1,5-dihydroxy-5-ethyl-2-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-1-methoxy-2-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(1-methoxy-4-hydroxy-4-ethyl-2-hexyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-4-hydroxy-4-ethyl-2-hexyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20-(4-ethyl-4-hydroxy-1-hexyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19)17(20)(Z)-tetraene;

1(S),3(R)-Dihydroxy-20-(5-ethyl-5-hydroxy-1-heptyn-1-yl)-9,10-seco-pregna-5(Z),7(E)-10(19),17(20)(Z)-tetraene;

1(S),3(R)-Dihydroxy-20-(6-ethyl-6-hydroxy-1-octyn-1-yl)-9,10-seco-pregna-5(Z),7(E),10(19),17(20)(Z)-tetraene;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-4,4-difluoro-5-hydroxy-heptyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4,4-dichloro-5-hydroxy-5-methyl-hexyloxy)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4,4-difluoro-5-hydroxy-5-methyl-hexyloxy)-9,10-seco-pregna-5(Z),7(E)-10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-fluoro-4-methyl-pentyl-oxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-ethyl-4-fluoro-hexyl-oxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(5-fluoro-5-methyl-hexyl-oxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R),20(S)-Trihydroxy-20-(4-ethyl-4-hydroxy-1-hexyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-methoxy-20-(4-ethyl-4-hydroxy-1-hexyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-ethoxy-20-(4-ethyl-4-hydroxy-1-hexyl)-9,10-secopregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(S)-[3-(2-hydroxy-2-methyl-1-propoxy)-prop-1E-en-1-yl]-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(4-ethyl-4-hydroxy-1-hexylthio)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-[5-methyl-5-hydroxy-1-hexylthio] -9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-[3-(1-methyl-1-hydroxyethyl)benzylthio]-9,10-seco-pregna-5(Z),7E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-methyl-3-hydroxy-1-butylthio)-9,10-seco-pregna-5(Z)-7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxy-hept-1(E)-en-3-yn-1-yl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

24-oxo-1(S),3(R),25-Trihydroxy-20(S)-9,10-seco-cholesta-5(Z),7(E),10,19-triene;

1(S),3(R)-Dihydroxy-20(R)-(3-oxo-4-hydroxy-4-ethyl-1-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(5-methyl-5-hydroxy-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(4-ethyl-4-hydroxy-hexyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(4-ethyl-4-hydroxy-hex-2-ynyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(4-hydroxy-4-methylpentyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(4-hydroxy-4-methylpent)-2-yn-1-yloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20-methyl-18-(3,1-hydroxy-1-methylethyl)phenylmethyloxy)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R)-Dihydroxy-20(R)-(1-methoxy-4-hydroxy-4-methyl-1-pentyl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene; isomer A;

1(S),3(R)-Dihydroxy-20(R)-(1-ethoxy-4-hydroxy-4-methyl-1-pentyl) -9,10-seco-pregna-5(Z),7(E),10(19)-triene; isomer A;

1(S),3(R),25-Trihydroxy-(20(S)-9,10-seco-cholesta-5(Z),7(E),10(19),23(E)-tetraene;

1(S),3(R)-Dihydroxy-(20(S)-(6'-hydroxy-6'-methyl-4'(E)-hepten-1'yl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene;

1(S),3(R),22(S),25-Tetrahydroxy-20(R),9,10-seco-cholesta-5(Z),7(E),10(19),23(E)-tetraene;

22(S)-Ethoxy-1(S)-3(R),25-trihydroxy-10(R)-,9,10-seco-cholesta-5(Z),7(E),10(1,23(E)-tetraene;

1(S),3(R)-Dihydroxy-20(S)-(3-(1-hydroxy-1-methylethyl)phenoxymethyl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(R) isomer;

1(S),3(R)-Dihydroxy-20(S)-(3-(1-hydroxy-1-methylethyl)phenylthiomethyl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(R) isomer;

1(S),3(R)-Dihydroxy-20(S)-(4-hydroxy-4-methylpent-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxyhept-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(S) isomer;

1(S),3(R)-Dihydroxy-20(R)-(5-ethyl-5-hydroxyhepta-1(E),3(E)-dien-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene or the corresponding 20(S) isomer;

1(S),3(R)-Dihydroxy-20(R)-(3-cyclopropyl-3-hydroxyprop-1(E)-en-1-yl)-9,10-secopregna-5(Z),7(E),10(19),16-tetraene (24(S) isomer) or the corresponding 24(R) isomer;

1(S),3(R)-Dihydroxy-20(1,5-dihydroxy-5-ethyl-2-heptyn-1-yl)-9,10-secopregna-5(Z),7(E),10(19),17(20)Z-tetraene, both 22-isomers.

Solubilizer

As mentioned above, a composition according to the invention contains a non-ionic solubilizer capable of solubilizing the active substance. The solubilizer contains polyoxyethylene groups and has no negative effect on the stability of the active substance in the final composition. The final composition is preferably in the form of an aqueous solution. In general, a parenteral administration form in the form of a solution is very advantageous, e.g., because i) a quicker onset of the effect, ii) a better reproducibility, and iii) compared with compositions also in the the form of solutions but containing a cosolvent, less pain on the injection site after injection.

Some surfactants (i.e. substances which, at low concentrations, adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface or interfacial tension) also have a function as solubilizing agents.

Solubilization can be defined as the preparation of a thermodynamically stable isotropic solution of a substance normally insoluble or very slightly soluble in a given solvent by the introduction of an additional amphiphilic component or components. Solubilization normally takes place by formation of micelles (i.e. the solubilizer must be present in a concentration above their critical micelle concentration) and the location of the solubilized molecule in a micelle may be *inter alia* i) on the surface at the micelle-solvent interface, ii) between the hydrophilic groups, or iii) in the micelle inner core.

A non-ionic solubilizer is a solubilizer where the hydrophile part of the solubilizer carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene groups.

A non-ionic solubilizer for use in pharmaceutical compositions according to the invention is typically a low histamine-releaser, i.e. a substance which e.g. in dogs and cats on first exposure releases at the most 1/10 of histamine compared to Cremophor ® EL. Methods for use in determining the histamine release are found e.g. in Lorenz, W. et al. in Agents and Actions, 1982, **12 1/2**, 64-80 and in Ennis, M. et al. in Agents and Actions, 1985, **16 3/4**, 265-268.

A non-ionic solubilizer for use in pharmaceutical compositions according to the invention contains typically a hydrophobic part and a hydrophilic part, such as about 70% w/w of a hydrophobic part and about 30% w/w of a hydrophilic part.

A non-ionic solubilizer suitable for use in a pharmaceutical composition according to the invention is a polyethylene glycol ester optionally in admixture with a polyethylene glycol. The polyethylene glycol and/or the polyethylene glycol part of the polyethylene glycol ester generally have a molecular weight of from about 200 to about 4000.

More specifically, the polyethylene glycol ester is a polyethylene glycol hydroxystearate such as a polyethylene glycol 12-hydroxystearate and the polyethylene glycol hydroxystearate may be or is a monoester, a diester or a mixture thereof.

As mentioned above, a pharmaceutical composition according to the invention may further comprise polyethylene glycol. In preferred embodiments of the invention the polyethylene glycol and/or the polyethylene glycol part of the polyethylene glycol ester suitable for use in compositions according to the invention have a molecular weight of from about 200 to about 800.

An especially suitable solubilizer for use in a pharmaceutical composition according to the invention is a solubilizer comprising polyethylene glycol 660 hydroxystearate such as, e.g. Solutol® HS15. Solutol® HS15 is manufactured by BASF, cf. Technical Information ME 151 e (977) July 1998 (MPM) from BASF Fine Chemicals, and contains about 65-70% of polyglycolester of 12-hydroxystearic acid as a hydrophobic part and about 25-30% of polyethylene glycol as a hydrophilic part. The main fatty acid component of Solutol® HS15 is 12-hydroxystearic acid, where also stearic and palmitic acid are present in detectable amounts. Free polyethylene glycol is present as well as its mono- and di-esters, and a further 2-3% of the 12-hydroxy group has been etherified with ethylene oxide. Solutol® HS15 has been proven to be especially suitable for use as a solubilizer in compositions according to the invention. However, other combinations of polyethylene glycolesters of 12-hydroxystearic acid, stearic acid, palmitic acid and/or polyethylene glycol as well as use of polyethylene glycolesters and/or polyethylene glycols having other molecular weights than those relevant for Solutol® HS15, are of course within the scope of the present invention.

In general, a non-ionic solubilizer for use in compositions according to the invention has a HLB value of at least about 12.

The concentration of the non-ionic solubilizer in a composition according to the invention is intended to be as low as possible (so as to avoid any significant negative influence after administration), normally within a range of from about 0.001% to about 30% w/v such as, e.g. from about 0.005% to about 25% w/v, from about 0.01 to about

20% w/v, from about 0.01 to about 15%, from about 0.01% to about 10% w/v, from about 0.01% to about 8% w/v, from about 0.05% to about 6% w/v, from about 0.05% to about 5% w/v, from about 0.1% to about 3% w/v, from about 0.2% to about 2% w/v, from about 0.3% to about 1.5% w/v or from about 0.4% to about 1% w/v such as, e.g. about 0.5% w/v.

Aqueous vehicle

A composition according to the invention comprises an aqueous vehicle. The aqueous vehicle contains of course water, but it may furthermore also contain pH adjusting agents, stabilizing agents, solubilizing agent (cf. above), isotonic adjusting agents, solvents (e.g. organic solvents; as discussed below, a composition according to the invention is most suitably formulated without any content of organic solvent, but in some cases it may be appropriate to include an organic solvent as well), etc. The concentration of water in a composition according to the invention is normally at least about from about 65% to about 99% w/w.

In contrast to prior art compositions, it is not mandatory that the aqueous vehicle of a composition according to the invention contains any chelating agent, ethanol and/or another organic solvent.

The pH in a composition according to the present invention is normally within the physiological range, i.e. it is in a range of from about 7.0 to about 9.0 such as, e.g. from about 7.2 to about 8.5, from about 7.3 to about 8.0, from about 7.3 to about 7.8, from about 7.4 to about 7.6 such as, e.g., 7.4 or 7.5.

In interesting embodiments of the invention, a composition comprises from about 0.0001% to about 0.01% w/v of Seocalcitol and from about 0.1% to about 1.5% w/v of Solutol® HS 15 or from about 0.0005% to about 0.0025% w/v of Seocalcitol and from about 0.2% to about 1.0% w/v of Solutol® HS 15.

A pharmaceutical composition according to the invention may further comprise an antioxidant. Especially suitable are antioxidants which have a solubility in water which is at least 1.5 times greater than their solubility in the non-ionic solubilizer. Relevant examples are sodium ascorbate, sodium bisulfite, sodium sulfite and mixtures thereof.

In the present context it is important that the antioxidant is soluble in water. In a composition according to the invention, a part of the active substance is present in the aqueous medium in soluble form and any oxidation takes place in this medium. On the

contrary, if the antioxidant is fat-soluble, it is contemplated that the antioxidant and the active substance would compete on the space within the micelles resulting in a decrease in the solubility of the active substance.

The concentration of an antioxidant - such as, e.g., sodium ascorbate - when present in a composition according to the invention, is from about 0.2% to about 3% w/v such as, e.g., from about 0.3% to about 2.5% w/v or from about 0.4 to about 2.0% w/v such as, e.g., about 0.5% w/v in the final composition.

As appears from the Examples herein, a specific embodiment of the invention is a pharmaceutical composition containing

10 µg	Seocalcitol
15.4 mg	disodium phosphate dihydrate
2 mg	sodium dihydrogen phosphate dihydrate
0.8 mg	sodium chloride
5 mg	sodium ascorbate
5 mg	Solutol® HS 15

ad 1 ml water for injection.

Use of the compositions according to the invention

A composition according to the present invention containing a vitamin D or a vitamin D analogue like those substances described above, is suitable for use in the treatment and/or prophylaxis of:

i) diseases or conditions characterized by abnormal cell differentiation and/or cell proliferation such as, e.g., psoriasis and other disturbances of keratinisation, HIV-associated dermatoses, wound healing, neoplastic diseases and cancer. Specific examples of neoplastic diseases are hepatomas, pancreas, mamma, colon and prostata cancer as well as hematological neoplastic disorders and skin cancer, and

ii) diseases of, or imbalance in, the immune system such as host-versus-graft and graft-versus-host reaction and transplant rejection, and auto-immune diseases such as discoid and systemic lupus erythematosus, diabetes mellitus and chronic dermatoses of auto-immune type e.g. scleroderma and pemphigus vulgaris, and

iii) inflammatory diseases such as rheumatoid arthritis

as well as in the treatment and/or prophylaxis of a number of other diseases or disease states, including hyperparathyroidism, particularly secondary hyperparathyroidism associated with renal failure, cognitive impairment or senile dementia (Alzheimer´s disease) and other neurodegenerative diseases, hypertension, acne, alopecia, skin atrophy e.g. steroid induced skin atrophy, skin ageing, including photo-ageing, and in promoting osteogenesis and treating/preventing osteoporosis and osteosmalacia.

The composition according to the invention is especially suited for treatment of cell proliferative disorders; disorders of the calcium metabolism, such as renal osteodystrophy, hypoparathyreoidism, vitamin D resistant hypophosphataemic rachitis, or osteomalacia; or neoplastic diseases, such as hepatomas, cancer of the pancreas, mamma, colon or prostata, or a hematological neoplastic disorder; where the method of treatment comprises administering to a patient in need thereof a composition according to the invention.

Administration routes for the compositions according to the invention

As mentioned in the introductory part, a composition according to the invention is intended for parenteral use, i.e. for use by injection into e.g. an animal or human body. The application may be by the intraveneous, intramuscular and subcutaneous route, the intraveneous route being preferred for compositions suitable for use in connection with neoplastic disorders.

However, whenever relevant, compositions according to the invention may also be suitable for use by other administration routes such as, e.g., the oral route, the topical route and the nasal route. In such cases, a person skilled in the art can make any necessary adjustments with respect to the concentration of the active substance and with respect to the other ingredients included in the composition.

A composition according to the invention is normally presented as an aqueous solution. However, in certain cases such as, e.g., in connection with the administration of a composition by the topical or oral route, a composition according to the invention is a liquid composition which may be presented in the form of a solution or a gel.

Apart from the active substance and an aqueous vehicle, a composition according to the invention may contain pharmaceutically or cosmetically acceptable excipients such as, e.g., preservatives like e.g. parabens, such as methyl, ethyl or propyl p-

hydroxybenzoate, benzalkonium chloride and benzylalcohol, antioxidants as discussed above, chelating agents, e.g. EDTA, citric acid and phosphoric acid, flavouring agents, gelling agents such as, e.g., water-soluble cellulose derivatives and carbomers.

A composition according to the invention may be presented in the form of a unit dose (e.g. in ampoules) or a multiple-unit dose composition (i.e. in vials containing two or more doses).

Dosage

In general the concentration of the active substance in the composition and the dosis will depend on the condition to be treated or prevented and the desired or necessary administration frequency. The concentration of the active substance in a pharmaceutical composition depends on the nature of the second compound in question, its potency, the severity of the disease to be prevented or treated, and the age and condition of the patient. Methods applicable to selecting relevant concentrations of the active substance in the pharmaceutical compositions are well known to a person skilled in the art and may be performed according to established guidelines for good clinical practice (GCP) or Investigational New Drug Exemption ("IND") regulations as described in e.g. CPMC/E.U. Guidelines for Good Clinical Practice 95/135. A person skilled in the art would, by use of the methods described in standard textbooks, guidelines and regulations as described above as well as common general knowledge within the field, be able to select the exact dosage regimen to be implemented for any active substance and dosage form using merely routine experimentation procedures.

In embodiments containing Seocalcitol as the active substance, a dosage of about 1-100 µg is suitable.

Other aspects of the invention

The invention also relates to a method for preparing the compositions according to the invention. Details concerning the preparation are given in the Examples herein. Furthermore the invention relates to use of a non-ionic solubilizer as a stabilizing agent, a method for administering an active substance to e.g. a human, the method comprising administering to a human in need thereof a therapeutically and/or prophylactically effective amount of the active substance in a pharmaceutical composition according to the invention and to a method for the treatment and/or prophylaxis of a neoplastic disease.

As will be understood, details and particulars concerning the composition aspects of the invention will be the same as or analogous to the details and particulars concerning the other aspects of the invention, and this means that wherever appropriate, the statements above concerning a pharmaceutical composition apply mutatis mutandis to all aspects of the invention.

The invention is illustrated further in the following, non-limiting examples.

EXAMPLES

Example 1

Preparation of an aqueous pharmaceutical composition according to the invention

An aqueous solution for parenteral administration is prepared as follows

Ingredients (all pharmacopoeial grade)	per ml
Seocalcitol (active substance)	10 µg
Disodium phosphate dihydrate (buffer)	15.4 mg
Sodium dihydrogen phosphate dihydrate (buffer)	2 mg
Sodium chloride	0.8 mg
Sodium ascorbate (antioxidant)	5 mg
Solutol® HS 15 from BASF (solubilizer)	5 mg
Water for injection	ad 1 ml

Solutol® HS 15 is dissolved in the water for injection by heating it to a temperature of at the most 80°C. A cover of nitrogen is applied. The buffer substances and the sodium chloride are added and then the solution is cooled to at the most 30°C. Then sodium ascorbate is added and, finally, Seocalcitol is dissolved in the solution obtained.

The solution is subjected to sterile filtration and is autoclaved at an appropriate time-temperature condition.

Example 2

Chemical stability of Seocalcitol in aqueous pharmaceutical compositions

The chemical stability of Seocalcitol in aqueous solutions was investigated in order to determine whether pharmaceutically acceptable excipients generally used have any influence on the stability. pH in the present aqueous solutions was adjusted to pH=7.5. In the presence of ascorbate but without N_2 cover the pH value decreased to 7.1 - 7.2 within a short period of time.

Seocalcitol is a vitamin D analogue which is susceptible to degradation in an aqueous acidic environment. Thus, the degradation rate is lowered by a factor of about 25 when pH is shifted from acidic pH to neutral-weakly alkaline pH. When acid is present, Seocalcitol may be degraded by an allyl inversion, or Seocalcitol may be decomposed.

The decay of Seocalcitol was monitored by use of a HPLC method employing a 125 mm x 4 mm column packed with LiChrospher RP-18, 5 µm and a mobile phase of acetonitril : 0.01 M phosphate buffer pH 6.0 (60:40). The flow rate was 2 ml/min, 500 µl of a sample was injected and the effluent was monitored at UV-264 nm.

The influence on the degradation of Seocalcitol was determined for the following excipients:

Solubilizer:	Tween 20 and Solutol® HS 15
Concentration of solubilizer:	5 mg/ml and 10 mg/ml
Sodium ascorbate (antioxidant)	0 mg/ml and 10 mg/ml
EDTA (chelating agent)	0 mg/ml and 1 mg/ml
Nitrogen cover	- (0) and + (1)

The following experiments were performed:

Table 1

Degradation in % after storage for 3 months at 25°C

Batch No.	solubilizer	solubilizer conc. mg/ml	Ascorbate mg/ml	EDTA mg/ml	Nitrogen	Degr. (%) at 25°C
9625813	Tween 20	10	10	0	0	0
9625814	Tween 20	5	0	0	0	13.57

Batch No.	solubilizer	solubilizer conc. mg/ml	Ascorbate mg/ml	EDTA mg/ml	Nitrogen	Degr. (%) at 25°C
9625815	Tween 20	10	10	1	1	0.68
9625816	Tween 20	5	10	0	1	0
9625817	Tween 20	5	10	1	0	0.3
9625818	Tween 20	5	0	1	1	17.4
9625819	Tween 20	10	0	1	0	27.05
9625820	Tween 20	10	0	0	1	8.73
9617911	Solutol HS15	10	10	0	0	0
9617912	Solutol HS15	5	0	0	0	5.79
9617913	Solutol HS15	10	10	1	1	0.35
9617914	Solutol HS15	5	10	0	1	0
9617915	Solutol HS15	5	10	1	0	1.27
9617916	Solutol HS15	5	0	1	1	5.42
9617917	Solutol HS15	10	0	1	0	8.62
9617918	Solutol HS15	10	0	0	1	3.17

Table 2

Degradation in % after 3 months at 25°C in formulations without ascorbate

Batch No.	solubilizer	Solubilizer conc. mg/ml	Ascorbate mg/ml	EDTA mg/ml	Nitrogen	Degr. (%) at 25°C
9625814	Tween 20	5	0	0	0	13.57
9625818	Tween 20	5	0	1	1	17.4
9625819	Tween 20	10	0	1	0	27.05
9625820	Tween 20	10	0	0	1	8.73
9617912	Solutol HS15	5	0	0	0	5.79
9617916	Solutol HS15	5	0	1	1	5.42
9617917	Solutol HS15	10	0	1	0	8.62
9617918	Solutol HS15	10	0	0	1	3.17

Table 3

Degradation in % after 3 months at 25°C in formulations with ascorbate

Batch No.	Solubilizer	Solubilizer conc. mg/ml	Ascorbate mg/ml	EDTA mg/ml	Nitrogen	Degr. (%) at 25°C
9625813	Tween 20	10	10	0	0	0
9625815	Tween 20	10	10	1	1	0.66
9625816	Tween 20	5	10	0	1	0
9625817	Tween 20	5	10	1	0	0.3
9617911	Solutol HS15	10	10	0	0	0
9617913	Solutol HS15	10	10	1	1	0.35
9617914	Solutol HS15	5	10	0	1	0
9617915	Solutol HS15	5	10	1	0	1.27

Degradation after 3 months at 25°C (Table 1-3):

The results indicate that solutions containing Solutol® HS 15 are more stable than solutions containing Tween 20 as solubilizer. Thus, e.g. the decay of the Seocalcitol in solutions without any content of ascorbate, EDTA and without any nitrogen cover but containing 5 mg/ml of Tween 20 or Solutol® HS 15, respectively, was 13.57% and 5.79%, respectively.

Furthermore, the results indicate that EDTA has a negative effect on the stability of Seocalcitol in solutions containing Solutol® HS 15 as solubilizer and ascorbate (see e.g. Table 3 and compare the results from batch No. 9615817 with the results from batch No. 9617915). Normally, EDTA is used in solutions containing substances which are susceptible to oxidative degradation in order to enable a complexation of any metal ions which may accelerate the oxidative degradation. However, the results obtained indicate that compositions containing Solutol® HS 15 may be sufficiently stabilized against oxidative degradation by using ascorbate and, thus, avoiding any further stabilizing agent present in the solution. In other words, the results indicate that it is possible to formulate a composition in soluble form with a content of very few pharmaceutically acceptable excipients. Such compositions are of course especially needed in those cases where the compositions are intended for injection directly into the circulatory system (any side effect of an excipient becomes of course more pronounced when a composition containing the excipient is injected directly into the circulatory system).

In short, the results show that solutions containing sodium ascorbate lead to significantly less degradation of Seocalcitol. The same applies to solutions containing Solutol® HS 15, whereas solutions containing EDTA have no positive effect on the stability of Seocalcitol.

Overall conclusion

To ensure an appropriate stability of Seocalcitol, the presence of sodium ascorbate is necessary. At 25°C, Solutol® HS 15 has a much better effect on the stability than Tween 20, especially for solutions without sodium ascorbate.

Example 3

Improvement of the chemical stability of Seocalcitol - comparison of the stability of two different compositions of Seocalcitol

The stability of the compositions from Example 2 containing Seocalcitol solubilized in an aqueous vehicle without any content of organic solvent and containing Solutol® HS 15 as a solubilizer (Table 4) was compared with the stability of compositions of Seocalcitol containing a co-solvent of ethanol-propylene glycol (Table 5) and having a content of Seocalcitol of 10 or 30 µg. The compositions containing co-solvent were adjusted to a specific pH value (in a range of 6.8 - 9.2) in order to investigate the influence of pH on the stability of the compositions. An example of the constitution of a co-solvent composition having a pH of about 9 is given in the following:

Seocalcitol	10 or 30 µg
Disodium phosphate dihydrate	1.8 mg
Sodium chloride	3.88 mg
Benzyl alcohol	15.675 mg
Ethanol 99.9%	79.2 mg
Propylene glycol	414 mg
Water for injection to make 1 ml	

The stability of the various compositions was determined after 3 months of storage at a temperature of 40°C and the results are given in the following Tables 4-5.

Seocalcitol injection

Stability data for solubilized and cosolvent formulations

Table 4

Solutol® HS15

Batch No.	pH	Ascorbate added mg/ml	Degradation (%) after 3 months at 40°C	Comments
9617911	7.2	10	.1.09	30mcg active/ml; without Nitrogen
9617913	7.4	10	1.5	30mcg active/ml; with Nitrogen; + EDTA
9617914	7.4	10	0	30mcg active/ml; with Nitrogen
9617915	7.2	10	3.5	30mcg active/ml; without Nitrogen + EDTA
9634916	7.5	5	0	10mcg active/ml; without Nitrogen
9634917	7.2	5	0.14	30mcg active/ml; without Nitrogen
9822012	7.5	5	2.2	10mcg active/ml; with Nitrogen; autoclaved
9634915	7.3	1	0	10mcg active/ml; without Nitrogen
9634918	7.3	1	2.2	30mcg active/ml; without Nitrogen

Table 5

Cosolvent

Batch No.	pH of the water part	Degr. (%) after 3 months at 40°C	Comments
9524911	6.83	16	10mcg active/ml
9524912	7.55	6.23	10mcg active/ml
9524913	9.16	0.39	10mcg active/ml
9524214	6.78	6.18	10mcg active/ml
9608211	9.04	1.59	10mcg active/ml
9608711	8.97	1.23	10mcg active/ml
9626611A	8.99	2.66	10mcg active/ml; autoclaved
9626611B	8.99	2.07	10mcg active/ml; autoclaved
9530211	7.5	4.53	30mcg active/ml
9530212	7.58	3.73	30mcg active/ml
9605911	9.01	2.2	30mcg active/ml
9606511	9.17	0.78	30mcg active/ml

The results show that compositions containing co-solvent are more susceptible to degradation than compositions without co-solvent (i.e. compositions containing a solubilizer, especially compositions containing Solutol® HS 15). Thus, in order to obtain a relatively low degree of degradation of Seocalcitol, the pH of the compositions containing co-solvent should be about 9. In contrast thereto, a pH of about 7-7.5 of compositions containing Solutol® HS 15 is acceptable in order to obtain a low degree of degradation of Seocalcitol (see Fig. 1).

In other words, by employment of a solubilizer like Solutol® HS 15, it is possible to obtain aqueous solutions of active substances having a relatively low solubility in water, and the compositions may be without any content of organic solvent (i.e. it is possible to obtain compositions without any content of organic solvent(s) or it is possible to significantly reduce the high content of organic solvent(s), which are present in a traditional co-solvent composition). Compositions according to the invention, i.e. compositions containing a solubilizer, may very advantageously be employed for parenteral use compared with compositions containing an organic solvent (e.g. in a relatively high amount) because an organic solvent in compositions intended for parenteral administration normally leads to side effects like pain (in connection with the administration) and to necrosis of tissue.

Furthermore, the results indicate that Solutol® HS 15 has a stabilizing effect on Seocalcitol. At pH 7.5, the degradation of Seocalcitol after 3 months storage at 40°C is 2.2% for a composition containing Solutol® HS 15 whereas it is 4.53% for a composition containing a co-solvent (i.e. without any solubilizer). With respect to compositions containing a co-solvent, an increase of pH to above about 9 seems to be necessary in order to obtain a degradation of Seocalcitol below 1% after 3 months storage at 40°C (see Fig. 2).

Conclusion

In other words, at the pH employed (pH 7.5) Solutol® HS 15 not only functions as a solubilizer but it also appears to function as a stabilizing agent and improves the chemical stability of Seocalcitol.

CLAIMS

1. An aqueous pharmaceutical composition for parenteral use, said composition comprising

i) as active substance a vitamin D or a vitamin D analogue having a solubility in water of ≤ 0.1% w/v at room temperature, and which is susceptible to degradation in an aqueous acidic environment,

ii) a non-ionic solubilizer capable of solubilizing said active substance, the solubilizer being a low histamine-releaser and containing a fatty acid ester of polyethylene glycol optionally in admixture with a polyethylene glycol and having no negative effect on the stability of the active substance in the final composition determined as described herein, and

iii) an aqueous vehicle.

2. A pharmaceutical composition according to claim 1, wherein the active substance is selected from the group of vitamin D and vitamin D analogues having a solubility in water at room temperature of ≤0.01% w/v, ≤0.001% w/v, ≤0.0001% w/v, ≤0.00001% w/v, ≤0.000007% w/v, ≤0.000005% w/v, ≤0.000003% w/v, ≤100µg/ml, ≤50 µg/ml, ≤25 µg/ml, ≤10 µg/ml, ≤5 µg/ml, ≤1µg/ml, ≤0.1µg/ml, ≤0.07µg/ml, ≤0,05 µg/ml, and ≤0.03 µg/ml.

3. A pharmaceutical composition according to claim 1, wherein the active substance is selected from the group consisting of Seocalcitol [1 (S),3(R)-dihydroxy20(R)-(5 '-ethyl-5 '-hydroxy-hepta-1 '(E),3 '(E)-diene-1 '-yl)-9,10-secopregna-5(Z),7(E),10(19)-triene] , α-calcidol, 1(S),3(R)-dihydroxy-20(R)-(5-ethyl-5-hydroxy-hept-1(E)-ene-3-yn-1-yl)-9,10-seco-pregna-5(Z),7(E),10(19)-triene, Calcipotriol, Calcitriol, and Tacalcitol, as well as mixtures thereof.

4. A pharmaceutical composition according to any of claims 1-3, wherein the non-ionic solubilizer is a fatty acid ester of polyethylene glycol in admixture with a polyethylene glycol and wherein the polyethylene glycol and/or the polyethylene glycol part of the fatty acid polyethylene glycol ester has a molecular weight of from about 200 to about 4000.

5. A pharmaceutical composition according to claim 4, wherein the fatty acid polyethylene glycol ester is a polyethylene glycol hydroxystearate such a polyethylene glycol 12-hydroxystearate.

6. A pharmaceutical composition according to claim 5, wherein the polyethylene glycol hydroxystearate is a monoester, a diester or a mixture thereof.

7. A pharmaceutical composition according to any of claims 4-6, wherein the polyethylene glycol and/or the polyethylene glycol part of the polyethylene glycol ester have a molecular weight of from about 200 to about 800.

8. A pharmaceutical composition according to any of the preceding claims wherein said non-ionic solubilizer comprises polyethylene glycol 660 hydroxystearate.

9. A pharmaceutical composition according to the preceding claim wherein the non-ionic solubilizer is Solutol® HS 15 as described in Technical Information ME 151 e (977) July 1998 (MPM) from BASF Fine Chemicals.

10. A pharmaceutical composition according to any one of claims 1-3, wherein the non-ionic solubilizer has an HLB value ≥ 12.

11. A pharmaceutical composition according to claim 1, wherein the non-ionic solubilizer is Solutol® HS 15 or polyethylene glycol 660 hydroxystearate.

12. A pharmaceutical composition according to any of the preceding claims, wherein the concentration of the non-ionic solubilizer is in a range of from about 0.001% w/v to about 30% w/v; preferably from about 0.005% w/v to about 25% w/v; or preferably from about 0.01% w/v to about 20% w/v, preferably to about 15%, more preferably to about 10% w/v, most preferably to about 8% w/v; more preferably from about 0.05% w/v to about 6% w/v, preferably to about 5% w/v; or more preferably from about 0.1% w/v to about 3% w/v, or more preferably from about 0.2% w/v to about 2% w/v; and most preferably from about 0.3% w/v to about 1.5% w/v; or most preferably from about 0.4% w/v to about 1% w/v; or the concentration of said non-ionic solubilizer is preferably about 0.5% w/v.

13. A pharmaceutical composition according to any of the preceding claims, wherein the active substance is Seocalcitol and the non-ionic solubilizer is Solutol® HS 15.

14. A pharmaceutical composition according to the preceding claim, the composition comprising from about 0.0001% w/v to about 0.01% w/v of Seocalcitol and from about 0.1% w/v to about 1.5% w/v of Solutol® HS 15, preferably from about 0.0005% w/v to about 0.008% w/v of Seocalcitol and from about 0.2% to about

1.0% w/v of Solutol® HS 15.

15. A pharmaceutical composition according to any of the preceding claims further comprising less than about 1 % w/w, preferably less than about 0.05% w/w, more preferably about 0.025% w/w, most preferably 0.01% w/w of a chelating agent.

16. A pharmaceutical composition according to any of the preceding claims, wherein the aqueous vehicle contain less than about 5% w/w , preferably less than about 4% w/w, preferably less than about 3% w/w, more preferably less than about 2% w/w, or most preferably less than about 1% w/w of an organic solvent.

17. A pharmaceutical composition according to the preceding claim, wherein the organic solvent is polyethylene glycol or polypropylene glycol.

18. A pharmaceutical composition according to any of the preceding claims, wherein the pH of the composition is in the range of from about 7.0 to about 9.0, preferably from about 7.0 to about 8.5, more preferably from about 7.0 to about 8.0, most preferably from about 7.0 to about 7.8.

19. A pharmaceutical composition according to any of the preceding claims further comprising an antioxidant which has a solubility in water which is at least 1.5 times greater than its solubility in the non-ionic solubilizer.

20. A pharmaceutical composition according to the preceding claim, wherein the antioxidant is selected from the group consisting of sodium ascorbate, sodium bisulfite, and sodium sulfite.

21. A pharmaceutical composition according to the preceding claim, wherein the concentration of sodium ascorbate in the final composition is from about 0.2% w/v to about 3% w/v, preferably from about 0.3% w/v to about 2.5% w/v, more preferably from about 0.4 % w/v to about 2.0% w/v, most preferably about 0.5% w/v.

22. Use of a (fatty acid) polyethylene glycol ester optionally in admixture with a polyethylene glycol and wherein the polyethylene glycol and/or the polyethylene glycol part of the polyethylene glycol ester has a molecular weight of from about 200 to about 4000 as a non-ionic solubilizer which is a low-histamine releaser as a stabilizing agent for therapeutically and/or prophylactically active substances which

are susceptible to degradation in an aqueous acidic environment.

23. Use according to claim 22, wherein the polyethylene glycol ester is a polyethylene glycol hydroxystearate, preferably a polyethylene glycol 12-hydroxystearate.

24. Use according to claim 23, wherein the polyethylene glycol hydroxystearate is a monoester, a diester or a mixture thereof.

25. Use according to any of claims 22-24, wherein the polyethylene glycol and/or the polyethylene glycol part of the polyethylene glycol ester has a molecular weight of from about 200 to about 800.

26. Use according to any of claims 22-25, wherein the non-ionic solubilizer comprises a polyethylene glycol 660 hydroxystearate.

27. Use according to any of claims 22-26, wherein the non-ionic solubilizer is Solutol® HS 15.

28. A method for the administration of an effective amount of a therapeutically and/or prophylactically active substance, preferably a vitamin D or a vitamin D analogue which has a solubility in water at room temperature of ≤ 0.1% w/v , or of a therapeutically and/or prophylactically active substance, preferably a vitamin D or a vitamin D analogue, selected from the group of substances having a solubility in water at room temperature of ≤0.01% w/v, ≤0.001% w/v, ≤0.0001% w/v, ≤0.00001% w/v, ≤0.000007% w/v, ≤0.000005% w/v, ≤0.000003% w/v, ≤100µg/ml, ≤50 µg/ml, ≤25 µg/ml, ≤10 µg/ml, ≤5 µg/ml, ≤1µg/ml, ≤0.1µg/ml, ≤0.07µg/ml, ≤0,05 µg/ml, and ≤0.03 µg/ml, and which is susceptible to degradation in an aqueous acidic environment, to a patient in need thereof, the method comprising injecting into the patient an aqueous pharmaceutical composition according to any of claims 1-21.

29. A method for the treatment of cell proliferative disorders, disorders of the calcium metabolism, or neoplastic diseases, the method comprising administering to a patient in need thereof a composition according to any of claims 1-21.

30. A method according to claim 29, wherein said neoplastic diseases are hepatomas; cancer of the pancreas, mamma, colon or prostata; or a hematological

neoplastic disorder.

31. A method according to claim 29, wherein said disorders of the calcium metabolism are renal osteodystrophy, hypoparathyreoidism, vitamin D resistant hypophosphataemic rachitis, or osteomalacia.

	Degr. in %	
pH	40C 3mths	40C 3mths
pH	Cosolvent	Solutol
6,83	16	
7,55	6,23	
9,16	0,39	
6,78	6,18	
9,04	1,59	
8,97	1,23	
8,99	2,66	
8,99	2,07	
7,5	4,53	
7,58	3,73	
9,01	2,2	
9,17	0,78	
7,15		1,09
7,4		1,5
7,4		0
7,15		3,5
7,5		0
7,2		0,14
7,5		0
7,3		0
7,3		0

Fig. 1

Seocalcitol degr. as a function of pH and formulation type

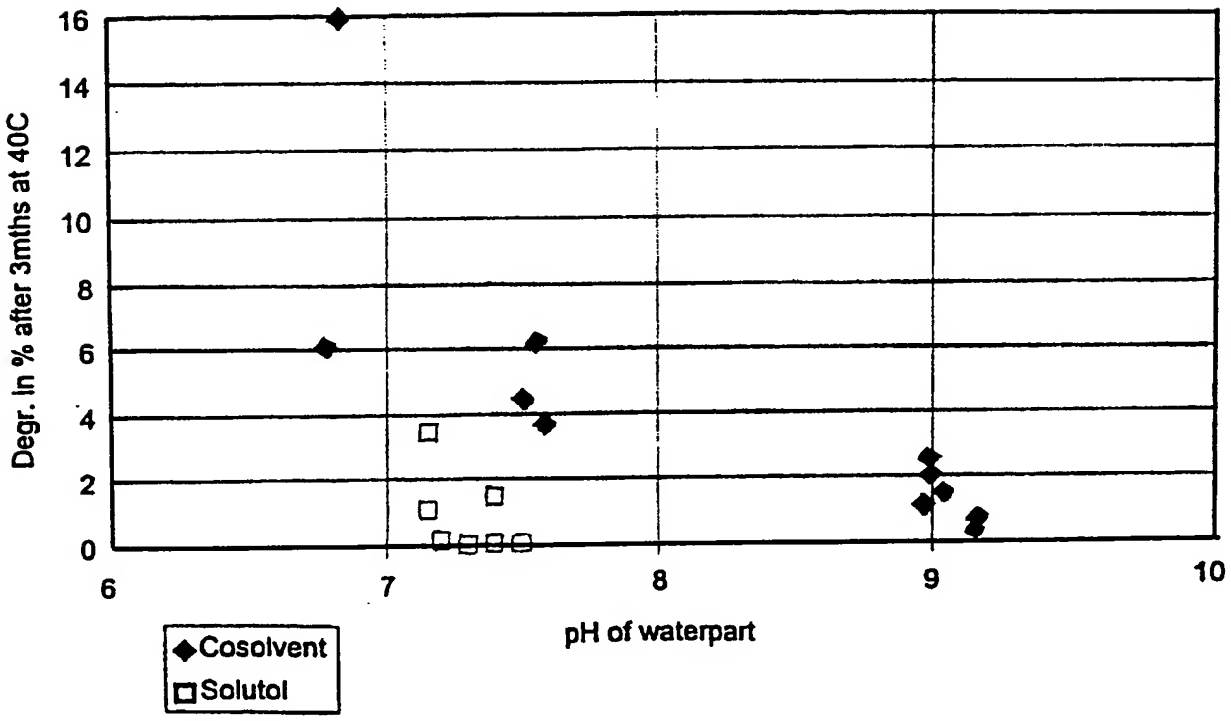

Fig. 2